FDA Oversight: Pancreatic Islet Cells

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FDA Regulation of Islets

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Dear Colleague:

The purpose of this letter is to inform or remind you of how the Food and Drug Administration (FDA) regulates allogeneic pancreatic islets for transplantation. **These cellular therapies are regulated as biological products subject to licensing under Section 351 of the Public Health Service Act** (PHS Act). 42 USC 262. They also meet the definition of "drug" in the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 USC 321(g), and are thus subject to certain requirements of the FD&C Act. An Investigational New Drug (IND) application should be submitted for review by FDA and be in effect prior to the initiation of clinical studies in humans of allogeneic pancreatic islets for transplantation.…

…

New Regulatory Approach for Cells and Tissues

- Provide a unified regulatory framework
- Provide greater flexibility and innovation in this field of medicine
- Provide a tiered regulatory approach with the level of regulation proportional to the degree of risk
- Risk determines level of regulation
  - Low Risk – tissues, Section 361, PHS
  - High Risk – Preapproval, Section 351, PHS or FD&C

The New "Tissue Rules"

- Establishment Registration & Product Listing Rule **(Final – 1/2001) – in effect**
  - Notify FDA of location and tissue products prepared
- Donor Eligibility Rule **(Final - 5/2004)**
  - Properly screen and test donors for communicable diseases
- Good Tissue Practices (GTP) Rule **(Final – 11/2004)**
  - Proper handling, processing and storage of tissue
  - Record keeping and facility cleaning
- **All effective May 25, 2005**

Definitions
21CFR 1271.3(d)(1)

- Human tissue derived from a human body and intended for transplantation into another human as defined in 1270.3(j)

Definitions
21 CFR 1270.3(j)

- Human tissue
  - (1)Intended for transplantation to another human for the diagnosis, cure, mitigation, treatment, or prevention of any condition or disease
  - (2)Recovered, processed, stored, or distributed by methods that do not change tissue function or characteristics
  - (3)Is not currently regulated as a drug, biologic, or device
  - (4)Excludes kidney, liver, heart, lung, pancreas, or any other vascularized human organ

Definitions
21 CFR 1271.3(d)(2)

- human cells, tissues, and cellular and tissue-based products (HCT/P's)
  - Articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient
- What is not an HCT/P?
  - Vascularized human organs for transplantation

Regulated Solely under Section 361, PHSA

- Minimally manipulated
- Homologous use only – advertising, labeling, intent
- Not combined with drug or device
  - Sterilizing, preserving, or storage agent
- Not systemic or metabolic activity
  - If yes, for autologous, 1st or 2nd blood relative, or reproductive use

What are Pancreatic Islet Cells?
Cell Therapy, Tissue, Organ?

- Fits the definition of an HCT/P
- Regulated article under 351 of PHS Act
  - More than minimal manipulation
  - Systemic and metabolic activity
  - Most are allogeneic
- Not a vascularized organ

Pancreatic Islet Cells are FDA regulated as a cell therapy

39 Active INDs

Islets as an FDA Licensed Product

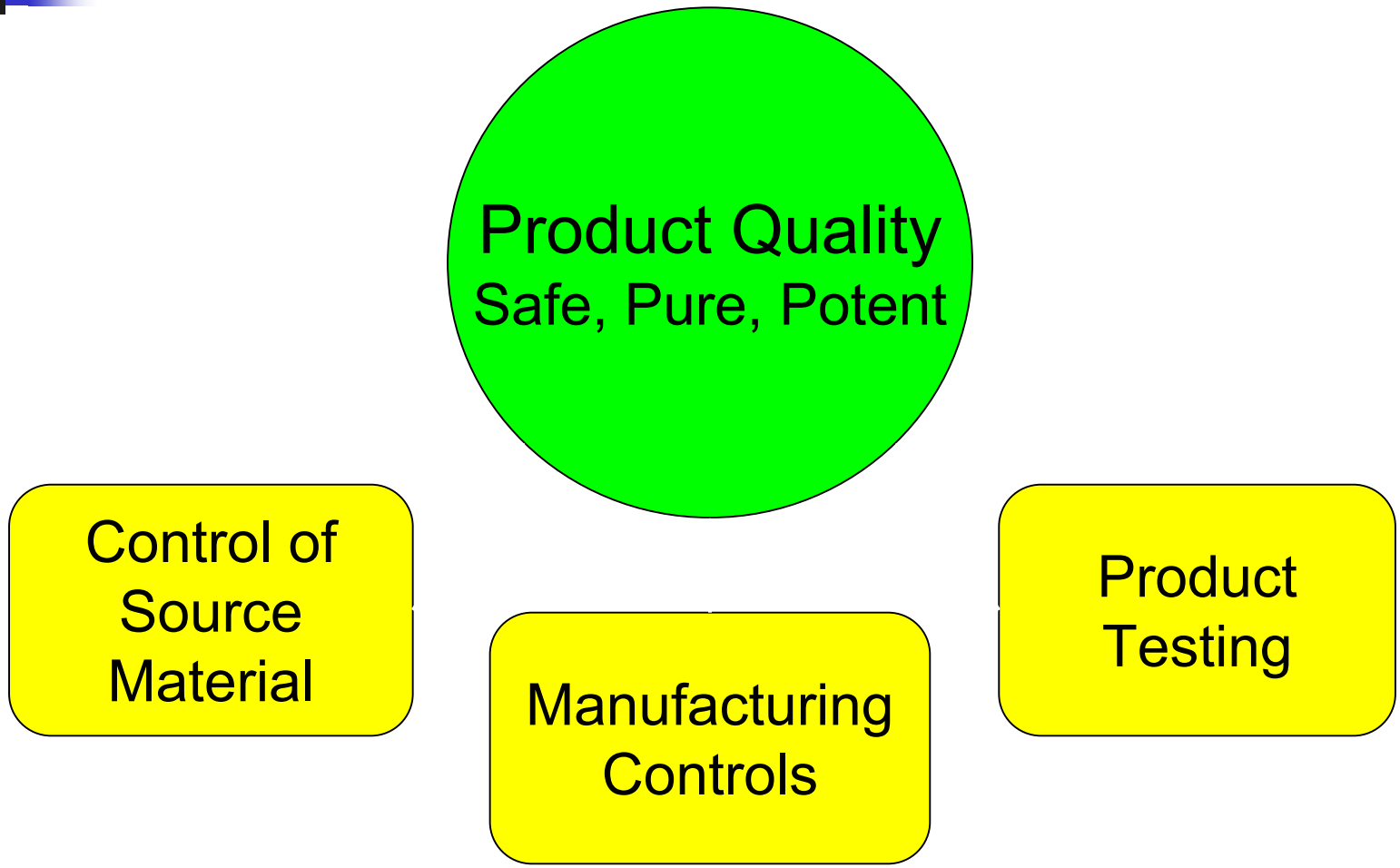
- What would be licensed?
  - The final islet cellular product
  - The manufacturing process is not licensed, however, a licensed product is dependent upon a specific manufacturing process
    - In the absence of extensive product characterization, the manufacturing process helps to define the final product

Biologics License Application

21 CFR 601.2:

The manufacturer…shall submit data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed requirements of *safety, purity, and potency*

Quality and Control



Source Material Control:
Islet source material is variable

Because the source material for islets are cadaveric organs, it cannot be controlled in a traditional way because:

- **Each organ is unique**
  - Organ size, donor age, extent of fibrosis and autolysis
- **Organ procurement procedures may vary**
  - Ischemia time, transport media, organ core temperature

Source Material Control:
Ensuring quality source material

A key component for ensuring control of a validated islet manufacturing process is the use of pre-defined acceptance criteria for the source material (donor organ).

Acceptance criteria should ensure that:

- suitable donor organs (organs with maximal potential for yielding adequate numbers of islets) are used for islet manufacturing
- unsuitable organs are excluded from further manufacture

Source Material Control:
Donor organ acceptance criteria

Acceptance criteria may include:

- Donor suitability determination
- Organ characteristics
- Harvesting conditions
- Transport conditions

Manufacturing Control:
Expectations

- In order to produce a product that is consistent in safety, purity, and potency the manufacturing process should be standardized and validated
- In-process testing should confirm the consistency of the process
- Licensed products, and the process by which they are made, are not experimental and have been shown to be safe and effective
  - Experimental procedures result in experimental products

Manufacturing Control:
Manufacturing changes

- Manufacturing changes can impact product safety, identity, purity, potency, consistency and stability in unforeseen ways.
- Therefore, the product used in pivotal trials should be representative of the product that is intended to be licensed.

Manufacturing Control:
Current status

- Investigators frequently “customize” an islet isolation procedure, based on a given donor organ’s characteristics, to optimize the yield of islets
- There are many variations in isolation methods; both within centers and across centers

Manufacturing Control:
Current status

- Examples of manufacturing variations include:
  - Digestion time and temperature
  - Use of additives such as DNase and protease inhibitors
  - Issues with the critical digestive enzyme (Liberase)
  - Culturing islets prior to transplantation

Manufacturing Control:
Finding a balance

- FDA agrees that some flexibility in the manufacturing process is acceptable, if conducted using predefined criteria or algorithms within a validated manufacturing protocol
- These predefined criteria would establish conditions that would allow for processing variations based on the characteristics of each donor organ

Product Testing:
Expectations

- Release testing should be performed on a sample of the final product
- Some test methods are prescribed by regulation, and some are proposed by the BLA applicant
- Each test result should contribute meaningful information about the safety, purity, and potency of the product

Product Testing:
Biological Product Standards

Part 610 Test	Test Method	Test Timing	Specification
Sterility	Specified	Final Product	Negative
Purity (pyrogenicity)	Specified	Final Product	Pass
Identity	Not Specified*	Final Product	Product Specific*
Potency	Not specified*	Final Product	Product Specific*

Summary – Product Considerations

- For licensure, a well-controlled, validated manufacturing process is needed to assure the safety, purity and potency of the final product
- This requires:
  - Control of all starting materials used
  - Control and consistency of the manufacturing process
  - Testing of the final product to verify it meets predefined product safety and quality standards

BLA Clinical Considerations

- ***Data must be sufficient to:***
  - ***assess risk-benefit***
  - ***describe use in a label***

"Adequate and Well-controlled"

- **"Adequate"**
  - ***Study agent standardized for identity, strength, quality, purity and dosage form,***
  - ***ie., "safety, purity, potency"***
  - ***An acceptable study design in which the protocol sufficiently describes dose/evaluation/endpoints/analyses***
  - ***Good Clinical Practice (verifiable data)***

Acceptable Safety

- **Subject characteristics**
  - ***ability to generalize to a population beyond those studied?***
- **Number of subjects/exposure**
  - ***ability to detect important but uncommon AE?***
- **Duration of follow-up**
  - ***sufficient for a chronic disease?***

Clinical Challenges addressed in clinical trials

- **Endpoints for studies intended to provide substantial evidence of efficacy**
- **Other clinical development concerns:**
  - ***requisite length of follow-up***
  - ***use of historical controls***
  - ***generalizability of data/requisite subjects***

FDA Oversight

- Meets FDA definitions of a regulated article
  - FD&C Act, Tissue Rules
- Many unknowns regarding use of islets
  - Control of product
    - Donor pancreas quality
    - Manufacturing process
    - Product testing
  - Safety and efficacy
- Only answered thru appropriate designed clinical and product development programs